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(54) Title: FOAMABLE FORMULATION AND FOAM

(57) Abstract

There is described a formulation comprising a foamable gelling agent (such as alginate, carageenan or carboxymethylcellulose gels) and a slow-release precipitant therefor. The precipitant is combined with the gelling agent during foaming and stabilises the foamed form of the gelling agent. Suitable precipitants include calcium salts such as calcium citrate and calcium chloride, or aluminium salts such as aluminium chloride. The increased stability of the foam facilitates sterilisation thereof. Further improvements can be obtained by exposing the cured foam to a precipitant applied externally, optionally washing, and then drying the foam. The foam of the present invention is suitable for medical or veterinary use and can include active ingredients for delivery to, for example, a wound site.

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1 FOAMABLE FORMULATION AND FOAM

2

3 The present invention is concerned with a foamable  
4 formulation and the foam formed therefrom.

5

6 A wide variety of gels, creams, ointments, lotions and  
7 other formulations are available for application to a  
8 body surface. The exact content of these compositions  
9 will vary depending upon the purpose of application.  
10 For example, a formulation may be applied to clean a  
11 body surface, to promote healing of any wound or  
12 injury, to prevent an exposed wound on the body from  
13 drying out, to prevent infection, etc. In certain  
14 circumstances the composition may include an active  
15 ingredient.

16

17 In our International Patent Application published 13  
18 June 1996 under No WO-A-96/17595 we describe a foamable  
19 formulation which comprises a foamable carrier or  
20 gelling agent, for example an alginate gel, and an  
21 active ingredient, such as a water soluble glass  
22 powder.

23

24 The product described in WO-A-96/17595 represented a  
25 considerable advance over the use of gel or cream.

1 We have now found that by including a precipitant for  
2 the gelling agent, in a slow-release form within the  
3 composition, further improvements with regard to the  
4 setting time of the foam and its stability can be  
5 achieved. In particular, the added stability enables a  
6 pre-foamed pad to be sterilised by irradiation,  
7 ethylene oxide, or other conventional means.

8

9 Thus, the present invention provides a formulation  
10 comprising a foamed gelling agent combined with a slow-  
11 release precipitant therefor. The gelling agent may be  
12 any agent capable of forming a foam, although  
13 preferably the gelling agent is physiologically  
14 compatible and non-irritant when maintained in contact  
15 with the body surface. The gelling agent may be a gel,  
16 for example a sodium alginate gel, carageenan gel,  
17 sodium carboxymethylcellulose gel or mixtures thereof.

18

19 The precipitant is desirably intimately admixed  
20 throughout the whole of the foamed gelling agent,  
21 preferably during the foaming process. In certain  
22 circumstances however the presence of the precipitant  
23 on one surface of the foamed gelling agent may be  
24 sufficient to cause stabilisation of the foam.  
25 Examples of precipitants include stabilising  
26 crosslinking agents which render the gelling agent  
27 insoluble. Examples include salts of polyvalent metal  
28 ions such as calcium, zinc, copper, silver or aluminium  
29 as well as borates, glyoxal and amino-formaldehyde  
30 precondensates. In one embodiment, the polyvalent  
31 metal ion may be released from a water-soluble glass  
32 which is admixed into the foamable carrier in  
33 comminuted form. A copper ion-releasing water soluble  
34 glass, a zinc-ion releasing water soluble glass and  
35 mixtures thereof are particularly of interest.

36

1 The role of the precipitant is to stabilise the foamed  
2 gel so that a stable foam is produced. Generally, the  
3 stable foam should be produced within a reasonable time  
4 period since if the precipitant is too slow-acting, the  
5 foam structure will have collapsed prior to  
6 stabilisation. However, a very fast acting precipitant  
7 may not allow sufficient time for the gel to be foamed.  
8 Desirably, the precipitant stabilises the foamed gel  
9 over a time period of 1 minute to 120 minutes,  
10 preferably within 30 minutes, and most preferably  
11 within 15 minutes at ambient temperature. The foam is  
12 considered to be "cured" when it can be lifted and  
13 carefully handled without collapse. The solubility of  
14 the precipitant and hence the setting (cure) time of  
15 the foam may be varied by adjusting the pH of the  
16 composition, especially where the precipitant is based  
17 upon a calcium salt. Generally, the solubility of a  
18 calcium salt will be increased by lowering the pH.  
19 Typical pH adjusters include organic acids such as  
20 acetic, adipic, citric, fumaric, lactic, alginic and  
21 tartaric acids. Usually an amount of 0.5 g to 5 g of  
22 organic acid per 100 gel is sufficient. The organic  
23 acid may be admixed with the precipitant prior to  
24 foaming or, more preferably, may be admixed with the  
25 gelling agent prior to foaming.

26  
27 Suitable precipitants include calcium citrate, calcium  
28 carbonate, calcium phosphate, calcium hydrogen  
29 phosphate ( $\text{CaHPO}_4$ ), aluminium chloride, barium  
30 carbonate, barium phosphate, barium sulphate, barium  
31 chloride and zinc carbonate.

32  
33 Where the gelling agent comprises an alginate gel, a  
34 carageenan gel or a carboxymethylcellulose gel one  
35 preferred precipitant is a calcium salt. Whilst  
36 calcium citrate has been used in the examples, other

1 slowly dissolving calcium salts are also suitable.

2

3 Where the gelling agent comprises  
4 carboxymethylcellulose gel one preferred precipitant is  
5 an aluminium salt.

6

7 In one embodiment the gelling agent and precipitant are  
8 packaged separately and only admixed during the foaming  
9 process or subsequent to foaming.

10

11 Alternatively, the precipitant may be included in a  
12 suspension (e.g. a suspension of calcium citrate and  
13 glycerine) which forms a separate layer on top of the  
14 gelling agent which remains substantially inert during  
15 handling and/or storage. Only once the operator  
16 desires to produce the foam, is the precipitant  
17 intimately admixed with the gelling agent (for example  
18 by shaking the container) and then promptly foamed.  
19 Using the precipitant in suspension form has the  
20 benefit that the suspension is easier to dispense from  
21 a pressurised container than a powder and also provides  
22 for more accurate dosing of unit precipitant per unit  
23 gelling agent.

24

25 Optionally, the formulation may comprise other  
26 additives such as decompactants which promote the  
27 desired foam structure or other foaming agents,  
28 plasticisers, humectants, preservatives, additives,  
29 sequestering agents or active ingredients such as  
30 antimicrobial agents, growth factors, hormones, living  
31 cells, etc.

32

33 The foam may be applied directly to the body area and  
34 allowed to produce a stable foam protective cover, for  
35 example over a wound. With the addition of the  
36 precipitants the cure of the foam is significantly

1 reduced, rendering the product more user friendly.

2

3 Alternatively, the foam can be produced onto a mould or  
4 other surface area, allowed to cure (for example by air  
5 drying or oven drying) and then applied to the body  
6 surface as a dressing. A foam sheet of this type is a  
7 preferred embodiment of the invention since it exhibits  
8 sufficient stability for easy handling whilst retaining  
9 a moist surface to promote wound healing. Optionally,  
10 the foam may be applied about a substrate (for example  
11 cloth, mesh, non-woven pad of alginate fibres, nylon,  
12 rayon, polylactid acid, polyglycolic acid,  
13 polycaprolactone or biocompatible glass fibres) which  
14 are then integrated into the foam pad produced.

15

16 As an example, the foam may be used to treat  
17 dermatological conditions (including psoriasis, atopic  
18 and allergic eczema). It may be convenient in this  
19 embodiment for the foam to deliver an active ingredient  
20 normally used to alleviate such conditions, for example  
21 a steroid such as hydrocortisone.

22

23 In another embodiment the foam may be used to treat  
24 burns or scalds, including sunburn.

25

26 In another embodiment the foam may be applied  
27 cosmetically, and for example may include skin  
28 moisturising agents, nutritional agents and growth  
29 factors suitable to promote skin regeneration. A foam  
30 intended for cosmetic use may include colorants or  
31 pigments so that the foam may be applied to the skin as  
32 a cosmetic or to disguise any blemishes in the skin.

33

34 The foam may be used prophylactically. In particular a  
35 foam containing a UV blocking agent may be applied to  
36 exposed areas of the skin to protect it from the

1 effects of the sun.

2

3 The formulation of the invention is applied to the body  
4 site of interest in the form of a foam and it is  
5 therefore essential that the composition undergoes a  
6 foaming process before application to the body. In the  
7 foaming process gas is forced into or is formed within  
8 the formulation to entrap small bubbles of gas therein,  
9 thereby forming the foam. Any suitably gas or gas  
10 producing system can be used to produce the foam.

11 Mention may be made of butane and nitrous oxide, but  
12 other gases like air, nitrogen, hydrofluorocarbons such  
13 as HFC134a or 227, hydrocarbons like propane,  
14 isopropane or a mixture thereof, are also suitable.  
15 Conveniently the foam may be produced by conventional  
16 means such as by using aerosol technology.

17

18 The formulation according to the present invention may  
19 be stored in any convenient container until required.  
20 Generally, the container will be designed to preserve  
21 the sterile nature of the formulation. Conveniently  
22 the container will be provided with means to foam the  
23 composition when required. Details are given in WO-A-  
24 96/17595. A two can packaging and dispensing system,  
25 as described in our co-pending UK Patent Application No  
26 9823029.5 (a copy of which is filed herewith), may be  
27 used to dispense the foam according to the present  
28 invention.

29

30 Generally, the foam will be produced from sterile  
31 ingredients.

32

33 Prior to the foaming process, the foamable carrier is  
34 preferably in the form of a gel. The gel may be  
35 sterilised and this is generally desirable where the  
36 foam is intended for medical use. Usually,

1     sterilisation will take place by autoclaving the  
2     formulation, since this is currently the most economic  
3     means of achieving sterilisation. Autoclaving at  
4     temperatures of from 100°C to 125°C for under ½ hour is  
5     normally sufficient. Generally, the autoclaving  
6     process should be as mild as possible, whilst being  
7     sufficient to sterilise the formulation. For example,  
8     autoclaving at temperatures of about 121°C for 15-20  
9     minutes is acceptable. The autoclaved formulation may  
10    then be foamed when cool. It is also possible,  
11    however, to sterilise the formulation by other means,  
12    for example by  $\gamma$ -irradiation or e-beam irradiation. It  
13    has been found that autoclaving the gel may cause the  
14    MW of the foamable carrier to be slightly reduced.  
15    Consequently it may be desirable to select a foamable  
16    carrier having a higher MW than that ultimately  
17    required.

18

19    The foam forms an air-tight cover around any wound or  
20    injury to which it is applied, and this prevents that  
21    area from drying out and may also combat infection.  
22    The advantages of applying a topical product in the  
23    form of a foam include:

24

- 25       1. Easy rapid application,
- 26       2. Conforms to surface irregularities,
- 27       3. Insulates the wound,
- 28       4. Cools the tissues,
- 29       5. Offers antibacterial action to prevent  
30          infection,
- 31       6. Biocompatibility with tissue,
- 32       7. Suitable for use as a vehicle for the  
33          administration of pharmaceutical agents,  
34          and/or
- 35       8. Maintains a moist environment.

36

1     Generally, the formulation of the present invention  
2     will be applied directly to the body site of interest  
3     in the form of a foam, the foam being produced from any  
4     suitable device (such as an aerosol) immediately before  
5     application. It is, however, possible for a quantity  
6     of the foamed formulation to be produced and then  
7     applied onto the body site by any suitable means, for  
8     example by hand or by spatula. This method may be  
9     required for wounds having a narrow opening.

10  
11    As stated above, the foam may also be produced on a  
12    suitable surface and then allowed to dry to produce a  
13    stable foam sheet which can be handled as described  
14    above without deterioration. Generally, the production  
15    of the sheet will take place under sterile conditions  
16    or may be sterilised after production. In the prior  
17    described foam product of WO-A-96/17595, it was not  
18    possible to provide a foamed pad product and then  
19    sterilise the pad by conventional means such as  $\gamma$ -  
20    irradiation, since it was found that the foam structure  
21    deteriorated during sterilisation. With the inclusion  
22    of the precipitant however, sterilisation of the  
23    pad is possible both by  $\gamma$ -irradiation, ethylene oxide  
24    sterilisation or other conventional means. This  
25    represents a very considerable advantage over the prior  
26    art product.

27  
28    The foam sheet is generally produced by foaming the  
29    foamable carrier in the presence of the precipitant and  
30    allowing the foam to cure, usually by simply exposing  
31    the foam to the atmosphere to air dry at ambient  
32    temperature. Optionally the foam may be dried at  
33    elevated temperatures, for example may be oven dried.  
34    Desirably, the cure time of the foam is 40 minutes or  
35    less at ambient temperature and preferably the foam  
36    cures within 15 minutes, for example within 10 minutes.

1 Where the foam sheet is to be sterilised, it is  
2 advantageous to pre-treat the sheet prior to  
3 sterilisation in order to further stabilise the sheet.  
4 The difficulty with sterilising any foam of the type  
5 described is that the foam structure tends to  
6 deteriorate and collapse during the sterilisation  
7 process. The pre-treatment of the sheet preferably  
8 involves impregnating the sheet with further  
9 precipitant. Conveniently, this may entail immersing  
10 the sheet in a bath of the precipitant or of a solution  
11 of the precipitant. For example, the sheet may be  
12 immersed in a bath of calcium chloride or calcium  
13 citrate. To ensure that the precipitant penetrates  
14 into the centre of the foam sheet, the sheet may be  
15 gently squeezed whilst immersed in the bath.  
16 Generally, immersion of the sheet for a short period of  
17 time, such as 2 to 3 minutes, is sufficient. The sheet  
18 may then be removed from the bath of precipitant,  
19 washed in a mixture of de-ionised water and glycerine  
20 to enhance moisture content and then dried. The  
21 stabilised foam sheet may then be sterilised by gamma  
22 radiation or through use of ethylene oxide.  
23  
24 The ratio of de-ionised water : glycerine in the wash  
25 stage is preferably 19:1 by volume.  
26  
27 The treated foam sheet is desirably oven dried at  
28 relatively low temperatures, for example 100°C or less,  
29 preferably approximately 35°C.  
30  
31 In a preferred embodiment the foamable carrier includes  
32 a combination of copper and zinc ions, optionally in  
33 the form of water soluble glass(es). We have found  
34 that a foam containing appropriate quantities of these  
35 metal ions are particularly resistant to the  
36 deleterious effects of sterilisation. We hypothesise

1 that the copper and zinc ions act as scavenger of free  
2 radicals produced in the foam during sterilisation and  
3 which are, we believe, responsible for the breakdown in  
4 structure of the foam. Additionally, both copper and  
5 zinc ions have a radioprotective effect. Consequently,  
6 we consider that any material known for its use as a  
7 free radical scavenger and/or as a radioprotectant may  
8 likewise exhibit a protective effect on the foam  
9 structure during sterilisation.

10  
11 Optionally the manufacture of a prefoamed product may  
12 envisage a continuous foaming process. The sheet may  
13 be divided into a convenient size and may be packaged.  
14 Optionally the foam sheet may be produced on contoured  
15 surface so that it is moulded to a pre-determined  
16 shape.

17  
18 Examples of suitable foamable gelling agents for use in  
19 the composition of the present invention include (but  
20 are not limited to) alginate and derivatives thereof,  
21 carboxymethylcellulose and derivatives thereof,  
22 collagen, polysaccharides (including, for example,  
23 dextran, dextran derivatives, pectin, starch, modified  
24 starches such as starches having additional carboxyl  
25 and/or carboxamide groups and/or having hydrophilic  
26 side-chains, cellulose and derivatives thereof), agar  
27 and derivatives thereof (such as agar stabilised with  
28 polyacrylamide), carageenan, polyethylene oxides,  
29 glycol methacrylates, gelatin, gums such as xanthum,  
30 guar, karaya, gellan, arabic, tragacanth and locust  
31 bean gum. Also suitable are the salts of the  
32 aforementioned carriers, for example, sodium alginate.  
33 Mixtures of any of the aforementioned gelling agents  
34 may also be used, as required.

35  
36 Preferred foamable gelling agents include alginate,

1 carageenan, carboxymethylcellulose, the derivatives and  
2 salts thereof and mixtures of any of these. Alginate  
3 (the derivatives or salts thereof, such as sodium and  
4 calcium alginate) are especially preferred. Foamable  
5 gelling agents having a molecular weight of from 10,000  
6 to 200,000 kDa are preferred, especially over 100,000  
7 kDa, for example 150,000 to 200,000 kDa, may be used.  
8

9 The formulation may further comprise a foaming agent,  
10 which promotes the formation of the foam. Any agent  
11 having a surfactant character may be used. The  
12 surfactants may be cationic, non-ionic or anionic.  
13 Examples of suitable foaming agents include cetrimide,  
14 lecithin, soaps, silicones and the like. Commercially  
15 available surfactants such as Tween™ are also suitable.  
16 Cetrimide (which additionally has an anti-bacterial  
17 activity) is especially preferred.

18 The formulation of the present invention (and thus the  
19 foam) may be used to deliver pharmaceutically active  
20 agents, in particular to deliver such agents in a  
21 controlled release manner. Mention may be made of:  
22

23  
24       Antiseptics, Antibacterials and Antifungal agents,  
25       such as Chlorhexidine, acetic acid, polynoxylin,  
26       povidone iodine, mercurochrome phenoxyethanol,  
27       acridene, silver nitrate, dyes eg brilliant green,  
28       undecanoic acid, silver sulphadiazine, silver  
29       proteins and other silver compounds,  
30       metronidazole, benzalconium chloride;

31  
32       Nutritional agents, such as vitamins and proteins;

33  
34       Growth factors and healing agents, including  
35       Ketanserin a serotonergic blocking agent;

1       Living Cells;

2

3       Enzymes include streptokinase and streptodormase;

4

5       Elements - zinc, selenium, cerium, copper,  
6       manganese, cobalt, boron, arsenic, chromium  
7       silver, gold, gallium;

8

9       Charcoal;

10

11       Desloughing and Debriding agents such as  
12       hypochlorite and hydrogen peroxide;

13

14       Astringents including potassium permanganate;

15

16       Antibiotics exemplified by neomycin and framycetin  
17       sulphate, sulfamylon, fusidic acid, mupirocin,  
18       bacitracin, gramicidin.

19

20       In addition the formulation of the present invention  
21       may further comprise other conventional additives such  
22       as plasticisers and humectants (such as glycerol,  
23       propane-1,2-diol, polypropylene glycol and other  
24       polyhydric alcohols), free radical scavengers to  
25       stabilise against the effects of sterilisation by  
26       irradiation, viscosity-adjusting agents, dyes and  
27       colorants, and the like.

28

29       Several experiments including comparatives tests have  
30       been made in order to demonstrate some of the  
31       advantages of the new compositions of the invention.  
32       Of course the embodiments described hereinbelow are  
33       submitted in order to better describe the invention and  
34       not to limit its scope.

35

36

1    EXAMPLE 12    PROCEDURE FOR MANUFACTURE OF UNIT BATCH (100 g) OF  
3    ALGINATE GEL4.  
5    Typically the alginate gels are made according to the  
6    following process:

- 7    1. De-ionised (DI) water is measured and poured  
8    into mixing vessel 1.
- 9    2. Desired amounts of suitable alginate (for  
10   example Keltone or Manucol) and glycerine are  
11   weighed using a calibrated balance, reading  
12   to 2 decimal places.
- 13   3. Alginate and glycerine are mixed together in a  
14   beaker until no lumps remain.
- 15   4. The whole alginate/glycerine mix is added very  
16   slowly to the water.
- 17   5. Once all the alginate/glycerine has been added to  
18   the water, the mixture is stirred until a smooth  
19   gel has formed.

20  
21   Several different alginate gels have been made  
22   according the above process. They differ and are  
23   referred to by the amount of alginate (for example  
24   Keltone) used. For example the alginate gel code 6½ has  
25   the following composition:

26

GEL CODE	6½
DI Water	80 ml
Glycerine	25.22 g
Keltone	6.5 g
Unit Batch Wt	111.72 g

32

33   The above composition can be varied to include other

1 weights of alginate, which would be reflected in the  
2 gel code number. For example a composition having 8g  
3 alginate (plus 80ml DI water and 25.22g glycerine)  
4 would be designated gel code 8. Analogous gel codes  
5 are used when other gel formers (eg carageenan or CMC)  
6 are substituted for the alginate in the above  
7 composition.

8

9 In one embodiment, the gelling agent may be present in  
10 the form of a suspension, for example a suspension in  
11 glycerine. To avoid diluting the gelling agent, the  
12 gelling agent suspension may be made up with less  
13 glycerine such that the total quantity of glycerine  
14 present in the gelling agent mixture and in the  
15 precipitant suspension adds up to the required amount.  
16 For example, the glycerine in the gelling agent mixture  
17 and precipitant suspension may be varied as follows:

18

19	Glycerine per 80 ml DI 20 water and 6 g alginate 21 (g)	Glycerine in precipitant suspension (g)
22	25.22	0
23	23.0	2.22
24	20.0	5.22
25	18.22	7.0
26	15.0	10.22

27

28 The above is illustrated with respect to a gel code 6  
29 composition, but the division of glycerine may be made  
30 for other gel code compositions, and is also not  
31 limited to the specific volumes illustrated above.

32

33

## 1    PROCEDURE FOR FOAM PRODUCTION

2

3    The propellant used to produce the foam can be  
4    compressed gases such as air, nitrogen, nitrous oxide  
5    or air, hydrofluorocarbons such HFC134a or 227 or  
6    hydrocarbons including propane, isopropane, n-butane,  
7    isobutane and 2-methylbutane.

8

9    Propellant vapour pressure can range from 0 to 110 PSIG  
10   at 70°C although the preferred range is 20 to 70 PSIG.  
11   Values within this range can be achieved for example by  
12   blending the three hydrocarbons propane, isobutane and  
13   butane. Calor Aerosol Propellants (CAP) sold by Calor  
14   Gas Ltd Slough may be used as propellant gas, when a  
15   blend of propane, isobutane and butane is used the  
16   proportions can be as follows:

17

18	<u>Grade</u>	<u>Propane %</u>	<u>Isobutane %</u>	<u>n Butane%</u>
19	CAP 30	11	29	60
20	CAP 40	22	24	54
21	CAP 70	55	15	30

22

23   A foam according to the invention can advantageously be  
24   produced following the following process:

- 25   1. 100 g of a gel according to the invention is  
26   poured to an aerosol canister.
- 27   2. 2.5 g of calcium citrate (food grade) is  
28   added to the canister.
- 29   3. A valve is crimped onto the canister.
- 30   4. Air is purged from the canister.
- 31   5. 4.5 g of propellant gas is added into the  
32   canister (65:35 CAP 40 : Isopentane  
33   propellant) and an actuator is positioned on  
34   the valve.
- 35   6. The canister is shaken vigorously for 20-30  
36   seconds.

1       7.     The canister is inverted and the foam dispensed.

2

3     EXAMPLE 2

4     Using a range of water-based gel formulations detailed  
5     below tests were done to improve the "setting" time and  
6     stability of the gel and its foam.

7

8     Preferred alginate compositions have an amount of  
9     alginate ranging from 5-9g in the composition set out  
10    in Example 1. Preferred alginates are Keltone HV and  
11    Manucol DMF.

12

13    Experiment 1. Gel Code 6% Alginate gel and foam mixed  
14    with calcium citrate compared to Gel Code 6% alginate  
15    gel alone

16

17    Foamed gel with calcium citrate

18    2.5 g calcium citrate was added to 100 g of gel and the  
19    foamed gel was spread out onto plastic sheeting. The  
20    resultant foam pad was liftable in 15 minutes.

21

22    Foamed gel without calcium citrate

23    The above experiment was reproduced by foaming the gel  
24    on its own as described above. The "setting" time of  
25    the foam was 10 hours.

26

27    The experiments were repeated using 100 g unfoamed gel  
28    with and without calcium citrate. Similar setting  
29    times to those observed for the foamed gels were  
30    obtained (15 minutes and 10 hours respectively) before  
31    the gel pads were liftable.

32

33    Conclusion: Calcium citrate speeds up and controls the  
34    setting time of the gel and the foam.

35

36    Experiment 2. Gel Code 8 Alginate gel mixed with water

1 soluble glass (WSG) containing phosphate and boron  
2 compared to gel code 8 alginate gel alone.

3

4 The WSG was comprised as follows:

5 28.5M% CaO

6 3M% Ag

7 5M% B<sub>2</sub>O<sub>3</sub>

8 18.5M% MgO

9 45M% P<sub>2</sub>O<sub>5</sub>

10

11 Foamed gel with WSG

12 2.5 g of WSG was mixed with 100 g gel and the foamed  
13 mixture was spread out onto plastic sheeting. The  
14 resultant foam pad was liftable in 120 mins.

15

16 Foamed gel without WSG

17 The above experiment was repeated by foaming the gel on  
18 its own. The "setting" time of the foam was  
19 approximately 10 hours.

20

21 The experiments were repeated using 100 g unfoamed gel  
22 with and without WSG. Similar setting times to those  
23 observed for the foamed gels were obtained (120 minutes  
24 and 10 hours respectively) before the gel pads were  
25 liftable.

26

27 Conclusion: WSG speeds up and controls the setting  
28 time of the gel and the foam.

29

30 **Experiment 3. Gel Code 4 Carageenan gel mixed with**  
31 **calcium citrate compared to gel code 4 gel alone**

32

33 Foamed gel with calcium citrate

34 3 g of calcium citrate was mixed with 100 g gel and the  
35 foamed mix was spread out onto plastic sheeting. The  
36 resultant foam pad was liftable in 120 mins.

1      Foamed gel without calcium citrate

2      The above experiment was repeated by foaming gel on its  
3      own as described above. The "setting" time of the foam  
4      was 10 hours.

5

6      The experiments were repeated using 100 g unfoamed gel  
7      with and without calcium citrate. Similar setting  
8      times to those observed for the foamed gels were  
9      obtained (120 minutes and 10 hours respectively) before  
10     the gel pads were liftable.

11

12     Experiment 4. Gel Code 4% Carageenan gel and gel code  
13     6% alginate gel mixed with calcium citrate compared to  
14     gel code 4% carageenan gel and gel code 6% alginate gel  
15     alone

16

17     Foamed gel with calcium citrate

18     2.5 g of calcium citrate was mixed with (50 g alginate  
19     and 50 g carageenan) gel and the foamed mix was spread  
20     out onto plastic sheeting. The resultant foam pad was  
21     liftable in 15 mins.

22

23     Foamed gel without calcium citrate

24     The above experiment was repeated by foaming the mixed  
25     gel on its own. The "setting" time of the foam pad was  
26     10 hours.

27

28     The experiments were repeated using 100 g unfoamed gel  
29     with and without calcium citrate. Similar setting  
30     times to those observed for the foamed gels were  
31     obtained (120 minutes and 10 hours respectively) before  
32     the gel pads were liftable.

33

34     Experiment 5. Gel Code 6% Alginate gel mixed with  
35     calcium citrate and added bentone IPM gel

36

1       2.5 g calcium citrate was added to 100 g of gel with 1g  
2       bentone IPM gel, admixed in an aerosol canister and  
3       dispensed therefrom as a foam onto a plastic surface.  
4       The resultant foam pad was liftable in 12 minutes.  
5       Bentone IPM gel is an admixture of isopropyl myristate,  
6       sterealkonium hectorite and propylene carbonate.

7  
8       Conclusion: Calcium citrate and bentone gel control  
9       the setting time of the foam. Bentone gel also acts as  
10      a reological agent and assists in the smoothness of  
11      delivery from the can.

12  
13      **Experiment 6. Gel Code 6% Alginate gel mixed with**  
14      **calcium citrate and added cetrimide**

15  
16      2.5 g calcium citrate was added to 100 g of alginate  
17      gel with 1g cetrimide in an aerosol canister and foamed  
18      onto a plastic surface. The resultant foam pad was  
19      liftable in 15 minutes.

20  
21      Conclusion: Calcium citrate speeds up the setting time  
22      of the foam. Cetrimide increases the cell structure of  
23      the product.

24  
25      **Experiment 7. Gel Code 6% Alginate gel mixed with**  
26      **calcium citrate and added Tween 20**

27  
28      2.5 g Calcium citrate was added to 100 g of alginate  
29      gel with 1g Tween 20 and foamed onto a plastic surface.  
30      The resultant foam pad was liftable in 12 minutes.

31  
32      Conclusion: Calcium citrate speeds up the setting time  
33      of the gel. The additive Tween 20 gave a much smoother  
34      delivery and an airier foam. Tween 80, 60 and 40 were  
35      also tried and all assisted in the delivery and product  
36      cell structure.

20

1      Experiment 8. Gel Code 4 Carboxmethyl cellulose and gel  
2      code 6½ alginate gel mixed with calcium citrate  
3      compared to the gel alone

4

5      2.5 g calcium citrate was added to (50 g CMC & 50 g  
6      alginate gel) and then the mixture was foamed onto a  
7      plastic surface. The resultant foam pad was liftable  
8      in 25 minutes. The gel foamed on its own was liftable  
9      overnight (approx. 10 hours).

10

11     Experiment 9. Gel Code 4 Carboxmethyl cellulose gel  
12     mixed with aluminium chloride compared with the gel  
13     alone

14

15     2 g aluminium chloride was mixed with 100 g CMC gel.  
16     The gel was spread onto a plastic surface. The  
17     resultant gel was liftable instantly. The gel alone was  
18     liftable overnight (approx. 10 hours).

19

20     Experiment 10. Gel Code 6 Alginate gel mixed with  
21     citric acid compared to gel code 6 alginate gel alone

22

23     2.5 g of citric acid was mixed with 100 g alginate gel  
24     and the mix was spread out onto plastic sheeting. The  
25     resultant gel pad was liftable in 120 mins. 100 g of  
26     the gel alone was spread onto plastic sheeting and the  
27     resultant pad was only liftable overnight (approx. 10  
28     hours).

29

30

31

32

33

34

35

36

1 Experiment 11. Gel Code 6% Alginate gel was mixed with  
 2 the following powders on a 100 g gel: 2.5 g powder  
 3 basis

	Powder	Results as a gel	Results as a foam
5	Calcium Chloride	Gel pad was formed instantly	Fast setting foam
7	Calcium Sulphate	Gel pad formed reasonably quickly	Foam set reasonably quickly
9	Aluminium Chloride	Gel pad formed instantly	Fast setting foam
11	Calcium Metaborate	Gel pad formed instantly	Fast setting foam

13

14

15 Experiment 12. Setting performances of a foam of a gel  
 16 code 6% alginate gel as a function of the amounts of  
 17 calcium citrate.

18

	Batch No	Amount of calcium citrate per 100 g gel	Result
20	DM02 210798	4 g	Not dispensed - set in can
21	DM03 210798	3 g	Very difficult to dispense. 9% minutes to set.
22	DM04 210798	2.5 g	Easier to dispense than above. 18% minutes to set
23	DM05 210798	2.25 g	Taking longer to set. 20 minutes.
24	DM02 200798	2 g	Setting time - 40 minutes

25

26

27

28

1      Experiment 13. Gel Code 6% alginate gel with calcium  
2      citrate and isopentane.

3

4      1.00g gel code 6% alginate gel was admixed with varying  
5      amounts of calcium citrate (2 to 4g), added to  
6      isopentane and mixed thoroughly before being spread  
7      onto a glass sheet. The isopentane vaporises at  
8      ambient temperatures and boils off through the gel  
9      leaving a foam pad of similar consistency to those  
10     produced by dispersion from an aerosol can. After  
11     half-an-hour the foam pads were liftable.

12

13     EXAMPLE 3

14

15     A. Gel code 5 alginate gel mixed with calcium citrate

16

17     The gel was prepared by mixing together alginate (5g  
18     Keltone HV), 20g glycerine and 80ml de-ionised water.  
19     5.22g glycerine was then added to 2.5g calcium citrate  
20     and a suspension of precipitant was created. The  
21     resultant gel and the suspension of precipitant were  
22     added to an aerosol can and a valve fitted. The can  
23     was purged of air, filled with 4.5g CAP 40 butane,  
24     shaken and dispensed. The foam produced was well mixed  
25     and set in 15 minutes.

26

27     B. Gel code 5 alginate gel mixed with calcium citrate

28

29     Experiment A was repeated using the same weight of  
30     Manucol LKX (5g) instead of Keltone HV. The resultant  
31     foam set within 12 minutes.

32

33     C. Gel code 5 alginate gel mixed with calcium citrate

34

35     The gel was prepared by mixing together alginate (5g  
36     Keltone HV), 20g glycerine and 80ml de-ionised water.

1       5.22g glycerine was then added to 2.5g calcium citrate  
2       and a suspension of precipitant was created. The  
3       resultant gel was added to the bottom can of the two  
4       can packaging system (see our co-pending UK Patent  
5       Application No 9823029.5) and the suspension or  
6       precipitant was added to the top can. The cans were  
7       prepared in the usual way. The two can packaging  
8       system was activated and the foam was dispensed. The  
9       foam produced was well mixed and set in 15 minutes.

10

11      D. Gel code 5 alginate gel mixed with calcium citrate

12

13      Experiment C was repeated using the same weight of  
14       Manucol LKX instead of Keltone HV. The resultant foam  
15       set within 12 minutes.

16

17      The set foam from A, B, C and D were then further  
18       processed by first immersing the foam in a solution of  
19       2.5% calcium chloride solution for 2 minutes, rinsing  
20       in de-ionised water and then finally rinsing in a 1%  
21       glycerine solution. The foam pads were then dried in  
22       the oven at 35°C and packaged in sterilisable pouches.

23

24      The resultant sterilised pads were compared with can  
25       reference 2 below (see Example 4). The foams produced  
26       in the two can system had a more even pore size  
27       throughout compared to those made in a one can system.  
28       Comparing the suspension with the powder/gel mix showed  
29       no difference in the structure of the final product.

30

31      EXAMPLE 4

32

33      A 1 litre batch of gel code 5 alginate gel was  
34       manufactured. Nine bottom cans of a two can packaging  
35       system as described in our co-pending UK Patent  
36       Application No 9823029.5 were filled with 100g gel in

1 each. Nine top cans were made up with varying powders  
2 as detailed below. The cans were prepared in their  
3 usual way. The two can packaging system was activated  
4 and the foam was dispensed.

5

6 Once cured the foams were processed by varying a) the  
7 concentration of the calcium chloride immersion  
8 solution and b) the final wash concentration of the  
9 glycerine solution. All samples were halved and then  
10 oven dried at 40°C. The first half sample was removed  
11 after 8 hours and the second half after 16 hours. Once  
12 the foam pads had been processed they were packaged in  
13 EtO sterilisable airtight packaging as soon as they  
14 came out of the oven. The samples were sent for EtO  
15 sterilisation and examined on their return.

Can Ref	Top Can Component	Ca Chloride Conc.	Glycerine Sol Conc.	Drying Time	Description of Alginic Pad After EtO Sterilisation
1	2.5 g Ca Citrate	1%	1%	8 hrs	Flexible, soft & sponge-like
				16 hrs	Flexible, soft & sponge-like
2	2.5 g Ca Citrate	2.5%	1%	8 hrs	Moist, flexible & sponge-like
				16 hrs	Flexible, soft & sponge-like
3	2.5 g Ca Citrate	5%	1%	8 hrs	Dry pad with limited flexibility
				16 hrs	Dry pad with limited flexibility
4	2.5 g Ca Citrate	2.5%	2%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
5	2.5 g Ca Citrate	2.5%	2.5%	8 hrs	Moist, flexible, sponge-like pad
				16 hrs	Moist, flexible, sponge-like pad
6	2.5 g Ca Citrate	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
7	2 g Ca Citrate 2 g Activated Charcoal	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
8	2 g Ca Citrate 2 g Cu/Zn WSG	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like
9	2.5 g Ca Citrate 2 g Povidone Iodine	2.5%	5%	8 hrs	Moist, flexible, soft & sponge-like
				16 hrs	Moist, flexible, soft & sponge-like

1  
1       EXAMPLE 5

2  
3       **Experiment A**

4  
5       A 600 g batch of gel code 5 was made up using Manucol  
6       DMF as the gelling agent. This batch was split into  
7       six equal parts and inserted into the bottom can of a  
8       dual can aerosol system. The top cans were made up  
9       containing 1.5 g calcium citrate and varying amounts of  
10      alginic acid (% g increments from 0 to 2½ g). Once  
11      preparation was complete the cans were foamed out  
12      simultaneously and the setting time for each foam was  
13      recorded.

14

15 16	Can Number	Gel Weight	Calcium Citrate Weight	Alginic Acid Weight	Setting Time
17	1	100 g	1.5 g	0 g	20 mins
18	2	100 g	1.5 g	0.5 g	16 mins
19	3	100 g	1.5 g	1.0 g	14 mins
20	4	100 g	1.5 g	1.5 g	10 mins
21	5	100 g	1.5 g	2.0 g	9 mins
22	6	100 g	1.5 g	2.5 g	8 mins

23

24

25       **Experiment B**

26

27       Three 100 g batches of gel code 5 was made up using  
28       Manucol DMF as the gelling agent with alginic acid  
29       incorporated (0 g, 1 g and 2 g added). Each batch was  
30       filled into bottom cans and top cans were made up  
31       containing 1.5 g calcium citrate. Once preparation  
32       complete the cans were foamed out simultaneously and  
33       the setting times for each can recorded.

34

Can Number	Gel Weight	Calcium Citrate Weight	Alginic Acid Weight	Setting Time
7 "	100 g	1.5 g	1 g	8 mins
8	100 g	1.5 g	2 g	6 mins
9	100 g	1.5 g	0 g	20 mins

1        CLAIMS

- 2
- 3        1. A physiologically acceptable formulation for  
4              application to a body as a foam, said formulation  
5              comprising a foamable gelling agent and a slow-  
6              release precipitant therefor, wherein said slow-  
7              release precipitant is combined with said gelling  
8              agent during the foaming thereof and stabilises  
9              the foamed form of the gelling agent.
- 10
- 11        2. A formulation as claimed in Claim 1 wherein said  
12              precipitant is packaged separately to said gelling  
13              agent prior to foaming.
- 14
- 15        3. A formulation as claimed in either one of Claims 1  
16              and 2 wherein said gelling agent is alginate,  
17              carboxymethylcellulose, collagen, a  
18              polysaccharide, agar, a polyethylene oxide, a  
19              glycol methacrylate, gelatin, a gum, or salts or  
20              derivatives of any of these, or mixtures thereof.
- 21
- 22        4. A formulation as claimed in Claim 3 wherein said  
23              gelling agent is alginate, carboxymethyl-  
24              cellulose, carageenan gel, the derivatives or  
25              salts thereof, or mixtures thereof.
- 26
- 27        5. A formulation as claimed in any one of Claims 1 to  
28              4, wherein said gelling agent has a molecular  
29              weight of from 10,000 to 200,000 kDa.
- 30
- 31        6. A formulation as claimed in any one of Claims 1 to  
32              5, wherein said precipitant is a salt of calcium,  
33              zinc, copper, silver or aluminium; borates;  
34              glyoxal; or amino-formaldehyde pre-condensates
- 35
- 36

- 1        7. A formulation as claimed in any one of Claims 1 to  
2                  6 further containing a foaming agent.  
3
- 4        8. A formulation as claimed in Claim 7 wherein said  
5                  foaming agent is cetrimide, lecithin, a soap,  
6                  silicone, a surfactant or the like.  
7
- 8        9. A formulation as claimed in any one of Claims 1 to  
9                  8 wherein the gelling agent comprises an alginate  
10                 gel, a carageenan gel or a carboxymethylcellulose  
11                 gel and wherein the precipitant is a calcium salt.  
12
- 13      10. A formulation as claimed in any one of Claims 1 to  
14                 8 wherein the gelling agent comprises  
15                 carboxymethylcellulose gel and wherein the  
16                 precipitant is an aluminium salt.  
17
- 18      11. A formulation as claimed in any one of Claims 1 to  
19                 10 further comprising an organic acid in an amount  
20                 of 0.5 g to 5.0 g per 100 g gelling agent.  
21
- 22      12. A physiologically acceptable foam comprising a  
23                 foamed gelling agent stabilised by a precipitant.  
24
- 25      13. The foam as claimed in Claim 12 in the form of a  
26                 cured foam sheet.  
27
- 28      14. A foam as claimed in Claim 12 wherein said  
29                 precipitant is packaged separately to said gelling  
30                 agent prior to foaming.  
31
- 32      15. A foam as claimed in any one of Claims 12 to 14  
33                 wherein said gelling agent is alginate,  
34                 carboxymethylcellulose, collagen, a  
35                 polysaccharide, agar, a polyethylene oxide, a  
36                 glycol methacrylate, gelatin, a gum, or salts or

- 1 derivatives of any of these, or mixtures thereof.
- 2
- 3 16. A foam as claimed in Claim 15 wherein said gelling  
4 agent is alginate, carboxymethyl-cellulose,  
5 carageenan gel, the derivatives or salts thereof,  
6 or mixtures thereof.
- 7
- 8 17. A foam as claimed in any one of Claims 12 to 16,  
9 wherein said gelling agent has a molecular weight  
10 of from 10,000 to 200,000 kDa.
- 11
- 12 18. A foam as claimed in any one of Claims 12 to 17,  
13 wherein said precipitant is a salt of calcium,  
14 zinc, copper, silver or aluminium; borates;  
15 glyoxal; or amino-formaldehyde pre-condensates
- 16
- 17 19. A foam as claimed in any one of Claims 12 to 18  
18 further containing a foaming agent.
- 19
- 20 20. A foam as claimed in Claim 19 wherein said foaming  
21 agent is cetrimide, lecithin, a soap, silicone, a  
22 surfactant or the like.
- 23
- 24 21. A process of sterilising a foam for medical or  
25 veterinary use, said process comprising:
- 26
- 27 a) foaming a formulation of Claims 1 to 11 and  
28 allowing said foamed formulation to cure;
- 29
- 30 b) treating said foam with precipitant;
- 31
- 32 c) optionally, washing said treated foam;
- 33
- 34 d) drying said treated form; and
- 35
- 36

1           e)    sterilising said dried foam by exposure to  $\gamma$ -  
2           irradiation or ethylene oxide.

3

4       22. The process of Claim 21 wherein said treated foam  
5           is washed in a de-ionised water/glycerine mixture  
6           prior to drying.

7

8       23. The process of either one of Claims 21 and 22  
9           wherein the treated foam is oven dried at  
10          temperatures below 100°C.

11

12      24. The process of any one of Claims 21 to 23 wherein  
13          the foam is immersed in a bath of calcium chloride  
14          or calcium citrate solution as precipitant.

15